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Chemoenzymatic synthesis of 5-Hydroxymethylfurfural (HMF) derived plasticizers by coupling HMF reduction with enzymatic esterification

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Abstract

Biobased plasticizers substitutes of phthalates have been synthetized from HMF and carboxylic acids (or esters) through a chemoenzymatic cascade process that involves as first step the reduction of 5-hydroxymethylfurfural into 2,5-bis(hydroxymethyl)furan (BHMF) followed by the esterification of BHMF with carboxylic acids (or esters) using a supported lipase (Novozim 435). The reduction of HMF into BHMF has been performed using monodispersed metallic Co nanoparticles with a thin carbon shell (Co@C) with high activity and selectivity. After optimization of reaction conditions (temperature, hydrogen pressure and solvent) was possible to achieve 97 % conversion of HMF with 99 % selectivity to BHMF after 2 h reaction time. The reduction of HMF and esterification of BHMF using carboxylic acids or vinyl esters as acyl donors by lipase have been optimized separately in batch and in fixed bed continuous reactors. The coupling of two flow reactors (for reduction and subsequent esterification) working under optimized reaction conditions allowed to obtain the

diesters of BHMF in ~90 yield, while no loss of activity during 60 h of operation was observed.

Keywords: 5-hydroxymethylfurfural, 2,5-bis(hydroxymethyl)furan, Co catalyst, lipase, chemoenzymatic cascade process

Introduction

Currently, most of the transport fuels and chemicals came from fossil resources mainly petroleum. However, its high demand, limited reserves leading towards rapid depletion and environmental pollution associated to its combustion has led researchers to look for new sources of energy and chemical products.

Considering that biomass constitutes a renewable carbon source in the nature, numerous scientific and industrial communities have focused its research in the production of high value added products and biofuels from non edible lignocellulose biomass as a renewable alternative. 5-Hydroxymethylfurfural (HMF) obtained by dehydration of hexoses, constitute one of the most important versatile platform molecule due to its broad range of potential applications in the biofuels and chemical industries. Numerous transformations of HMF such as, oxidation, reduction, etherification, alkylation, aldol condensation, acetalization, hydration, reductive amination, etc. have been reported in the last years.[1–5] Among them, the reduction of the formyl group of HMF to obtain the symmetrical diol 2,5-bis(hydroxymethyl)furan (BHMF), has received much attention.[6] BHMF find a wide range of application as building block in polymer industries, foams, crown ethers, and as intermediate in pharmaceuticals[7],[8] while can also be converted into biofuels additives such as 2,5-dimethylfuran and 2,5-dimethyltetrahydrofuran.[9] Additionally, it is known that fatty acid diesters of BHMF have applications as biodiesel additives[10] and nonionic surfactants.[11]

Moreover, diesters of BHMF involving carboxylic acids of lower chain length (C2-C10) can be used as a new class of biobased plasticizers that can be substitutes of phthalates derived from petroleum.[12] Contrarily to phthalates, BHMF diesters are nontoxic, biodegradable and present excellent compatibility with PVC.

Classically, conversion of HMF into BHMF has been successfully performed using stoichiometric amounts of salts of metal hydrides (i.e. $LiAlH_4$). However, the generation of high amount of wastes and the cost of metal hydrides are important disadvantages of the process especially for industries. As consequence, a variety of catalytic pathways including conventional hydrogenation, hydrogen transfer reactions, as well as photocatalytic and electrocatalytic reductions have been proposed to produce BHMF from HMF.[13]

Particularly, the chemoselective synthesis of BHMF from HMF using hydrogen as reducing agent and metals as hydrogenating catalysts is not an easy task, due to the polyfunctional nature of HMF containing C=O, C=C and C-O bonds all of them susceptible to react with hydrogen. Thus, besides the hydrogenation of the formyl group other competitive processes such as hydrogenation of the furan ring, the removal of hydroxyl or carbonyl group, and the ring opening of furan can take place leading to low selectivity to BHMF.

The catalytic hydrogenation of HMF into BHMF has been performed with variable success especially over supported noble metals catalysts[13] such as Au, Pd, Pt, Ru, and Ir (see Table S1), being the selectivity to BHMF mainly controlled by the nature of the catalyst and experimental conditions. However, there is an increasing interest in substituting noble metal catalysts by inexpensive non-noble metals (NNM) since it not only represents economic advantages but also represents a promising approach for a more sustainable chemistry. Nevertheless, the main disadvantages of non-noble metals are that more severe reaction conditions (particularly high

hydrogen pressures and temperatures) are required to achieve similar yields to those obtained with noble metals, while the catalyst is more prone to deactivation due to metal agglomeration and leaching processes.

A variety of supported mono and bimetallic nanoparticles based on Cu, Ni and Co have been reported for the reduction of HMF into BHMF with good success. However in most cases, hydrogen pressures up to 70 bar are required,[6] while in other cases such as Cu/ZnO,[14] high amount of catalyst is required or leaching of the active metal specie (Raney-Co or Co-400) is observed[15] (see Table S1). Therefore, the development of new catalysts based on non-noble metals that efficiently work under reaction conditions similar to those required for noble metals is highly desirable.

Recently our group has developed monodispersed metallic Co and CoNi nanoparticles with a thin carbon shell (Co@C and CoNi@C) that showed excellent activity and selectivity for the chemoselective reduction of nitroarenes under mild reaction conditions, as well as for reduction of levulinic acid into γ–valerolactone.[16],[17] It was showed that the main advantages of these nanoparticles as catalysts are that the carbon shell protect the Ni and Co metal nanoparticles from over oxidation, leaching and agglomeration. Interestingly, the nanoparticles can be prepared at a large scale in a facile way by the hydrothermal decomposition of a Co-EDTA complex or in the presence of glucose, and stored under ambient conditions for long time without apparent morphological and activity changes.

Therefore, due the simplicity of preparation of these non-noble metal nanoparticles and the good catalytic activity showed in hydrogenation reactions, here we studied the potential of Co@C for the selective conversion of HMF into BHMF and, for extension, in a variety of carbonyl compounds. Moreover, we have envisaged a

cascade reaction where the reduction of HMF into BHMF is coupled with its enzymatic esterification with acyl donors to produce the corresponding BHMF diesters, useful as plasticizers substitutes of phthalates (Scheme 1).

Results and discussion

Synthesis and characterization of Co@C nanoparticles

The Co@C catalyst was prepared through the hydrothermal decomposition of a Co-EDTA complex at 450 ºC under hydrogen atmosphere[16] (see Experimetal section). The XRD pattern (Figure S1) of this sample shows the diffraction peaks associated to metallic Co with *fcc* phase (predominant phase), where the diffraction lines Co (111), (200) and (220) (PDF code 96-900-8467) are observed at 44.2º, 51.5º and 75.8º. Moreover a small amount of hexagonal close-packed Co phase (*hcp* phase)(PDF code 96-900-8493) corresponding to Co (100) and Co(101) at 41.65º and 47.41º can be also observed. Since the Co-EDTA complex was decomposed and reduced at 450 ºC, and the Co hcp phase is more stable at lower temperature than Co fcc phase[18] it is no surprising the coexistence of both phases.[19]

The Raman spectroscopy study showed the presence of CoOx. As indicated in Figure S2 vibration modes of Co_3O_4 (F_{2g}, E_g, and A)[20] can be detected in the Raman spectra. Also, typical Raman signals of layered carbon, bands at 1315 cm^{-1} and 1592 cm^{-1}, which corresponding to the D and G bands, respectively can be observed.[21] The intensity ratio of the G and D band is about 0.8, suggesting the existence of high proportion of disorder in the structured carbon in Co@C nanoparticles,[22] which is confirmed by the absence of peaks between 2500 and 2800 cm-1 related to the 2D band.

The morphology of Co@C was characterized by electron microscopy. In Figure 1, FESEM and TEM images (Figures 1a and 1b respectively) showed that Co@C consists of nanoparticles with sizes ranging from 15 to 100 nm (see Figure S3 for more images and particle size distribution).

The high-resolution transmission electron microscopy (HRTEM) images (Figure 2a and b) show that Co nanoparticles are covered by thin carbon layers with thickness ranging from c.a. 1 to 10 nm. Lattice fringes corresponding to metallic Co (d_{111}=0.20 nm)[23] can be observed in the core of the nanoparticle, while lattice fringes corresponding to Co_3O_4 (d_{113} = 0.24 nm)[24] can be observed in the surface below the carbon layers. The elemental composition and distribution of the elements was studied by the energy dispersive spectroscopy (EDS) elemental mapping showing the presence of Co, C, O and Na which are regularly dispersed in the nanoparticles (Figures S4a-e) which contain about 95 wt% of Co. The structural characterization of the samples indicates the presence of Co@C nanoparticles with a core-shell structure with metallic Co as the core, CoOx patches on the surface of Co crystallites, and thin layered carbon as the shell.

Catalytic activity of Co@C for the reduction of HMF into BHMF

To test the activity and selectivity of the Co@C catalyst for the reduction of HMF into BHMF, the reaction was performed first at 90 °C under 20 bar of hydrogen using methanol as a solvent. A variety of compounds can be obtained as showed in Scheme 2. However as can be observed in Figure S5 and Table 1 (entry 1), BHMF (**2**) was obtained almost quantitatively in high selectivity (99%) after 6 h while the over reduced compounds **4** (5-methylfurfural) and **5** (5-methyl-2-furfuryl alcohol) were detected as traces. It has been observed that temperature plays an important role on the selectivity to BHMF, in such way that over reduction

reactions can be favored,[14] when increasing reaction temperatures.

The effect of reaction temperature on the products distribution over Co@C catalyst was determined by performing the reaction at 110 °C (entry 2, Table 1). As can be observed, the initial reaction rate was considerably increased (see Figure S6), while the selectivity was practically maintained. BHMF was obtained in 99 % yield after 3 h. On the other hand, good results were also obtained when decreasing hydrogen pressure to 10 bar (entry 3, Table 1, Figure 3) indicating that the hydrogenating activity of our Co catalyst is high under these conditions and the catalyst maintains its selectivity at high HMF conversions. Thus, 96 % yield with 99 % selectivity to BHMF (**2**) was achieved after 2 h, while minor amounts of 5-methyl-2-furfural (**4**) and 5-methyl-2-furfuryl alcohol (**5**) were detected in the reaction media. Moreover, we observed that upon increasing the reaction time up to 24 h the BHMF was stable and no further over reduction occurs under these reaction conditions. When the pressure of hydrogen was further decreased to 5 bar and temperature increased to 120 °C (entry 4, Table 1, and Figure S7) the reaction rate was decreased considerably, although 90 % yield of BHMF (**2**) with 99 % selectivity could be achieved. However, 24 h reaction time was required under these reaction conditions, making the process unacceptable.

Then, we selected 10 bar of hydrogen pressure and 110 °C as the reaction conditions for studying the performance and the nature of the working catalyst.

We said before, that an important characteristic of this catalyst was the presence of thin carbon layers that protects the Co nanoparticles for going into deep oxidation when exposed to air and allow their reduction at lower temperature. Then, to study the role of the thin carbon layers in the Co@C catalyst on the catalytic activity, we try to remove the carbon shell on the Co nanoparticles by

performing calcinations at 250 ºC and 450 ºC. Previous Raman studies[16] showed that part of the carbon layers still persist when the catalyst is calcined in air at 250 ºC (Co@C-250a) and naked Co and CoOx species can be detected on the surface of the nanoparticles. However, when the catalyst is calcined at 450 ºC (Co@C-450a) the carbon shell is practically removed, and Co_3O_4 is the only oxidized specie detected. As can be seen in Table 1 when the reaction was performed with the Co@C-250a sample a decrease of the catalytic activity was observed when compared with the starting Co@C catalyst (see entry 5, Table 1 and Figure S8) and a further decrease occurs with the sample calcined at 450 ºC (see entry 6, Table 1 and Figure S9). Moreover, as can be seen in Figure S9 a longer induction period for hydrogenation exists with the sample Co@C-450a with respect to the Co@C-250a sample and with respect to the original sample (Co@C) which contains the full thin carbon layers. The results indicate that the Co@C-250a can slowly be reduced during the reaction to Co^0, which is the active phase. However, when the Co catalyst is oxidized at higher temperatures giving Co_3O_4 this is very difficult to reduce and it shows much lower selectivity to BHMF. Then it is clear that the carbon layers protect the Co nanoparticles from oxidation by air and the metallic Co facilitates the reduction of the Co oxide patches formed on the metallic nanoparticles by activating the H_2. In fact, when we performed the reaction using Co_3O_4 sample pre-reduced with H_2 at 450 ºC, (Co_3O_4-R) (entry 7, Table 1, and Figure S10) the reaction rate was considerably lower than those exhibited by Co@C catalyst.

We have also prepared two Co-based samples by decomposition of metal-organic complexes. One sample labeled as (Co-BTC) was prepared by decomposition of a metal-organic framework (MOF) with trimesic acid as linker[17] and a sample based on Co nanoparticles supported on carbon (Co@C/C) was

prepared by decomposition of a cobalt(II) acetate–phenanthroline complex on carbon.[25] As can be observed in Table 1 (entries 8 and 9) the activity and selectivity of these samples were similar among them, and considerably lower than those exhibited by Co@C. Finally, a control experiment performed in absence of catalyst only gave 15 % HMF conversion after 24 h with 53 % selectivity to BHMF, being the acetal **3** the main byproduct detected (entry 10, Table 1).

When the results obtained with the Co@C for reduction of HMF into BHMF are compared with those previously reported using different non noble metal based catalysts (Table S1) one can observe that our catalyst is more active and can operate at lower pressure. Moreover, when compared Co@C with previously reported catalysts based on noble metals we can see that Co@C performs in a similar way in terms of activity and selectivity than catalysts based on Ru, Pt or Pd.

Stability and reusability of Co@C catalyst

To investigate if Co leaching occurs during the reaction, an additional experiment was carried out where the reduction of HMF was stopped after 30 min. At this point, the catalyst was removed in hot with a magnet and the reaction was continued for 6 additional hours. No further conversion was detected during this time (Figure S11).

The reusability of the catalyst was studied by recovering with a magnet the Co@C after carrying a first run, washing them thoroughly with methanol and reusing the catalyst under subsequent cycles after hydrogenation at 170 ^{o}C during 2 h. As can be seen in Figure 4 the conversion and selectivity were maintained after four consecutive runs. Although the reaction rate decreases after the first cycle (see Figure S12), 90% yield of BHMF could be still obtained when prolonging reaction

time to 4h during the fourth cycle. Additionally, TEM analysis of the used catalyst after the fourth cycle (Figure S13) indicates that the monodispersed Co nanoparticles are preserved after the recycle process showing the stability of the catalyst during the hydrogenation of HMF. Therefore, the loss of activity can be attributed to adsorption of organic material on the active sites. To check that, after the fourth cycle of reaction, the catalyst was extracted with methanol in a Soxhlet apparatus. The analysis of the organic material extracted by Soxhlet after the fourth reaction cycle (10 wt % organic respect to catalyst weight) showed that 60 wt % corresponds to BHMF, 35 wt % to HMF, and 5 wt % to 5-methyl-2-furfuryl alcohol. These results suggest that the adsorption of organic material on catalyst could be the cause of the catalyst decay. In fact, the activity and yield to BHMF were increased when the extracted catalyst was tested in reaction after reduction with H_2 at 170 ^oC during 2 h (see Figure S12).

Catalyst scope

Considering the excellent results obtained with the Co@C catalyst for the hydrogenation of HMF, we have explored the hydrogenation of different aldehydes including aromatic aldehydes with electron donating and electron withdrawing groups, aliphatic and heterocyclic aldehydes, as well as ketones (Table 2). High catalytic activity and selectivity were achieved in the hydrogenation of the aromatic aldehydes with electron donating and electron withdrawing groups (entries 1-3, Table 2), while dehalogenation product was not detected in the case of p-fluorobenzaldehyde (entry 3, Table 2). Other furanic aldehydes derived from biomass such as furfural, and 2-methyl furfural were easily reduced to the corresponding alcohols with high selectivity.

Of special industrial interest is the reduction of furfural into furfuryl alcohol (entry 4, Table 2), that is an important intermediate (production of resins, fibers, fine

chemicals, lysine, vitamin C, lubricants and dispersant agents) and which is commercially produced (400 10^3 Tm/y) using copper-chromite catalyst. We can see that the Co@C catalyst described here is able to produce furfuryl alcohol with selectivities of practically 100% at 99% conversion. The chemoselective hydrogenation of C=O bonds in the presence of double carbon-carbon bonds was studied in the hydrogenation of citronellal (3,7-dimethyl-6-octenal) to obtain citronellol, an important alcohol in the fragrance industries. In this case 98% yield with 100% selectivity to citronellol was obtained in 2 h (entry 6, Table 2). As expected, ketones afforded the corresponding secondary alcohols in lower yield than aldehydes and higher amount of catalyst and prolonged reaction time were required. Nevertheless, in all cases the selectivity to the corresponding alcohols were 100% (see entries 8-11, Table 2).

Influence of the solvent in the reduction of HMF into BHMF

As presented in the introduction, a goal of this work was also the possibility of coupling HMF reduction with the enzymatic esterification of the BHMF with carboxylic acids to produce biobased plasticizers substitutes of phthalates. As we have showed above, the first step, i.e. the reduction of HMF is achieved with good performance using Co@C in methanol as a solvent. However, solvents as methanol or ethanol are not adequate media for enzymes, where denaturalization of the biocatalyst can easily occur. Therefore, to optimize the cascade process, the study of the influence of the solvent on the catalytic activity and selectivity of the Co@C catalyst was undertaken.

Since it is known that in the case of HMF reduction, the nature of the solvent can play an important role on the catalyst activity and selectivity,[26] the catalytic activity of Co@C was studied in different solvents and the results are showed in

Table 3. As can be seen there, polar protic solvents such as methanol and isopropanol were the most adequate for performing the hydrogenation of HMF, while conversion decreased when polar aprotic solvents were used. These results agree with the reported results of reduction of HMF using Pt/MCM-41 [27] in where the influence of the solvent was related with the Lewis acidity and basicity. Thus, protic solvents such as methanol, capable of accepting electrons, are able to polarize the C=O group more strongly than polar aprotic solvents making the C=O more prone to hydrogenation. As can be observed in Table 3 the conversion obtained with 2-methyltetrahydrofuran (2-MTHF) and acetone were considerably lower than those obtained with protic solvents, while the selectivity with 2-MTHF was maintained high. In fact, when the amount of catalyst was increased, 95 % conversion with 96 % selectivity to BHMF (**2**) could be obtained (entry 5, Table 3). At this point we know the 2-MTHF could be used as a solvent, and this solvent can be compatible with the lipase enzyme required to perform the esterification reaction to give the corresponding plasticizers.

Synthesis of BHMF diesters trough a cascade process

Generally, esterification reactions can be performed with homogeneous and heterogeneous acid catalysts. However, the reaction requires high temperature and strong acids that are not the most adequate reaction conditions when furanic derivatives such as BHMF are involved. Indeed, the presence of strong acid catalysts can promote not only the degradation of the furanic derivative but self-oligomerization processes decreasing obviously the yield and selectivity of the desired product. Nevertheless, we have tested the esterification process between BHMF and hexanoic acid using a Nafion-silica composite (SAC-13) as heterogeneous acid catalyst since we have previously showed that SAC-13 was an active catalyst to perform esterification reactions[28]. The reaction was

performed at reflux of 2-methyltetrahydrofuran as a solvent (80 ºC) in presence of SAC-13. The reaction proceeded very slowly and after 24h reaction, only 10 % of diester was detected in the reaction media, while the molar balance was only 60 % indicating the formation of oligomers, as was said above. Since the direct esterification between BHMF and the carboxylic acid resulted unsuccessful, we intended the transesterification between a carboxylic acid methyl ester and BHMF. Transesterification reactions of carboxylic acid methyl esters with alcohols can be successfully carried out using heterogeneous basic catalysts such as alkaline earth oxides such as MgO,[29] however high reaction temperatures are usually required, which can be a drawback in the case of the transesterification using BHMF as a substrate. Nevertheless, we have tested here the transesterification reaction between methyl hexanoate and BHMF using MgO as heterogeneous basic catalyst. When the reaction was performed at reflux of 2-methyltetrahydrofuran, the reaction did not proceeded at all, while when the reaction was performed in absence of solvent at 120 ºC, the reaction media evolved rapidly dark, and after 2 h the conversion of BHMF was 50 % but the diester was not detected at all, indicating that polymerization of BHMF takes place under these reaction conditions.

All the above results, clearly evidence the high instability of BHMF and the difficulty to perform conventional esterification process with conventional acid and base catalysts.

An interesting alternative to catalytic esterification with inorganic or organic acid and base catalyst is the use of biocatalysts. The biocatalysts are able to work under mild reaction conditions, can achieve high selectivity to the desired product and are environmental friendly catalytic systems. Lipases are versatile biocatalyst that promote a variety of reactions such as esterification, transesterification and

amidation. Thus, commercial available Lipase B from *Candida antarctica* immobilized on macroporous acrylic resin (Novozym 435), has been described as an efficient biocatalyst in the (trans)esterification of HMF[30] and double esterification of BHMF with fatty acids as acyl donors.[10]

Considering these precedents, we designed a sequential stepwise process in which HMF is transformed into BHMF diesters, by the combination of a first chemocatalytic pathway, involving the hydrogenation of HMF using Co@C catalyst, followed by the biocatalytic esterification of the produced BHMF with acyl donors (i.e. short chain alkanic carboxylic acids, and esters) in the presence of immobilized lipase (Novozym 435) (Scheme 3).

Recently Lacatus et al.[10] have performed the esterification of BHMF with long chain fatty acids using a lipase (Novozym 435) as biocatalyst. The authors found that high yields of BHMF fatty acid diesters can be obtained using a variety of solvents such as 2-MTHF, 1,4-dioxane or acetone in the presence of molecular sieves. The authors showed that the presence of molecular sieves to remove the water contained in the enzyme as well as the water released during the esterification was decisive to obtain the BHMF fatty acid diesters in high yields.

Following this protocol, we studied firstly the biocatalytic esterification of BHMF with, n-hexanoic using the commercially supported lipase (Novozym 435). Since the reduction of HMF to BHMF was selectively performed using methanol as a solvent, we first intended the enzymatic esterification of BHMF with hexanoic acid using this solvent, although we know that highly polar solvent such as methanol could denature the enzyme.[31],[32] As expected, using methanol as a solvent, enzyme activity was suppressed and esterification of BHMF did not occurred satisfactory. Then, we selected 2-MTHF that was a good solvent for the first

hydrogenation step of HMF to BHMF and it can be an appropriate solvent for the esterification reaction as showed in Table 3. As can be seen in Figure 5, (5-(hydroxymethyl)furan-2-yl)methyl hexanoate (BHMF monoester) was quickly formed and further transformed to the corresponding furan 2,5-diylbis(methylene)dihexanoate (BHMF diester). After 11 h reaction time, 99 % yield of BHMF hexanoic acid diester was obtained. For comparison purposes the esterification of BHMF with hexanoic acid in 2-MTHF was performed using other commercial supported lipases such as a lipase from Pseudomonas Fluorencens immobilized in Sol-Gel-AK and a Lipase B from Candida Antarctica immobilized in Sol-Gel-AK on pumice which have showed high enzymatic activity in esterification reactions.[33],[34] The results showed that these biocatalyst exhibited very low activity in the esterification of BHMF under our reaction conditions, achieving BHMF conversion < 2 % after 11 h reaction time.

Then, we continued our study with Novozim 435 and at this point, we tested the global process starting from HMF. Thus, HMF was reduced under the conditions of entry 5 (Table 3) in the presence of Co@C catalyst at 110 ºC in 2-MTHF as a solvent. After 10 h reaction time, the heterogeneous catalyst was removed with a magnet, hexanoic acid, lipase Novozym 435, and molecular sieves were added to the reactor while the temperature was kept at 35 ºC. As can be seen in Table 4, excellent yield and selectivity to the corresponding BHMF diester of hexanoic acid were obtained. When the two step process was performed with butyric and octanoic acid (entries 2 and 4) excellent yields and selectivities to the corresponding diesters were also obtained. However, when acetic acid was used, the selectivity to diester was considerably lower than those achieved with the others acids, and a mixture of monoester (46%) and diester (47%) was obtained after 24 h reaction. In this case, the lower enzymatic activity can be attributed to

the higher acidity of the acetic acid which can cause a partial deactivation of lipase.[30]

To show the stability of the inorganic-enzimatic catalytic system, the two step process using hexanoic acid, was performed during three consecutive cycles. As can be observed in Table 5, deactivation of the Co@C, and the supported lipase catalyst occur, being necessary to increase the reaction time in order to achieve good total yields of the BHMF diester.

Although carboxylic acids are cheap and commercially available in a wide range, its use as reagents in esterification reactions have several disadvantages such as the water formation, poor solubility with alcohols, low reactivity and consequently large reaction times are required. Furthermore, the presence of water not only can affect the enzymatic activity of lipases but also it can act as a competitive nucleophilic reagent that has to be removed in order to achieve high performances. Moreover, the intrinsic acidity of the carboxylic acids can deactivate the enzyme.

To overcome these drawbacks vinyl esters of acids are usually used in transesterification reactions with lipases. Moreover, in this case, the enol leaving group rapidly tautomerizes to the keto form (acetaldehyde), thus no competitive nucleophilic attack occurs and the reaction becomes irreversible. Since vinyl esters are commercial available and widely used in polymerization processes, we tested the two step process using vinyl hexanoate as acyl donor. As can be seen in entry 5, Table 4, excellent yield (97 %) and selectivity to BHMF diester (100 %) was obtained in only 0.5 h during the second step using the enzime, being the final yield to diester of 89 %.

For comparison purposes we performed the preparation of 2,5-bis(acetoxymethyl)furan in one-pot process using a conventional acetylation

method.[35] For that, HMF was reduced in the presence of Co@C, using hydrogen and 2-MHF as a solvent, at 110 ^{o}C and 10 bar during 10h, achieving 93 % yield of BHMF. After that the Co@C catalyst was removed with a magnet and the required amount of pyridine and acetic anhydride was added and the mixture stirred at room temperature for 8h. After this time a total conversion of BHMF with a selectivity of 86% to diester was observed. After 24 h reaction time 90 % total yield of 2,5-bis(acetoxymethyl)furan could be obtained. These results show that working with carboxylic acid derivatives of high reactivity (such as anhydrides) it is possible to work under very mild reaction conditions avoiding subsequent degradation and polymerization of HMF. However, and important problem associated to this methodology is the generation of wastes during purification coming from the excess of anhydride and pyridine required for the reaction.

Synthesis of BHMF diesters in a fixed bed continuous flow reactor

We have showed that diesters plasticizers derived from HMF can be produced through a chemoenzimatic process in batch reactor. We have also studied the two step process by performing the reaction in a fixed bed continuous flow reactor system. To couple both steps in a continuous flow reactor, we studied first the continuous HMF reduction into BHMF using Co@C catalyst and 2-MTHF as a solvent. Unfortunately, deactivation of the catalyst was very fast and conversion of HMF decreased to 60 % after 2 h of operation. Then, as the deactivation of the catalyst was considerably lower when methanol was used as a solvent (see Figure 3) we used methanol in the continuous process. After optimization of temperature and flow rate (see Figure S14), excellent results in terms of conversion, selectivity and stability of the catalyst could be obtained working at 90 ^{o}C, with a flow rate of 12 mL h^{-1} (see Figure 6). The continuous flow reactor

was maintained during 60 h of operation without loss of activity giving and average yield of BHMF of ~90 %.

At this point we studied the esterification reaction of BHMF using vinyl hexanoate as acyl donor and supported lipase as catalyst in a flow reactor. In this case a solution of BHMF in 2-MTHF (1.5 wt%) and vinyl hexanoate (6.5 wt%) was feed in the continuous reactor at 35 ^{o}C and first the flow rate was optimized. As can be seen in Figure S15 the optimum flow rate was 12 mL h^{-1} which corresponds to a contact time of 2.1 h and a space velocity (WSHV) of 0.48 h^{-1}. Under these reaction conditions production of BHMF hexanoic acid diester was maintained in 98 % yield during 60 h of operation without loss of activity (see Figure 7).

Finally, we coupled both flow reactors working under optimized reaction conditions. Thus, in the first reactor Co@C catalyst was placed, and feed with a solution of HMF in methanol (1.5 wt%) (12 mL h^{-1}) at 90 ^{o}C under 10 bar of hydrogen during 60 h. At the end of the reaction the methanol was removed from the flow by evaporation, and a solution containing 1.3 wt % of BHMF and vinyl hexanoate (6 wt %) in 2-MTHF was used as feed for the second reactor where the lipase Novozym 435 was placed and heated at 35 ^{o}C. A 88 % total yield of diester was obtained without loss of activity during 60 h of operation (see Figure 8).

The results presented above show that it is feasible to couple both steps (HMF reduction-BHMF esterification) in a continuous process. Since the methanol has to be removed after the first step, a process could be envisaged in where methanol will be separated by flash evaporation after the first reduction reactor, and reused again in the first step of the process.

Conclusions

Diesters of 2,5-bis(hydroxymethyl)furan (BHMF), useful as plasticizers substitutes of phthalates, have been synthetized from 5-hydroxymethylfurfural (HMF) and carboxylic acids (or esters) through a chemoenzymatic cascade process. The process involves as first step the selective reduction of HMF into BHMF using a non-noble metal catalyst followed by the esterification of BHMF with acyl donor groups catalyzed by a commercial immobilized lipase (Novozym 435). The optimization of the HMF reduction (temperature, H_2 pressure and solvent) has shown that it is possible to obtain BHMF with excellent conversion (98 %) and selectivity (99 %) using a Co (Co@C) catalyst consisting of Co^0 nanoparticles coated with carbon layers. This catalyst has an activity and selectivity similar to catalysts based on noble metals, under moderate reaction conditions (110 ^oC and 10 bar H_2). By selecting the appropriate solvent, it has been possible to couple the reduction step with the esterification of the BHMF with different carboxylic acids as acyl group donors using the supported lipase (Novozym 435) in a batch mode reactor. However, deactivation of the lipase during consecutive reuses was observed which was attributed to denaturation of enzyme due to the intrinsic acidity of the carboxylic acid. Nevertheless, excellent results have been obtained in terms of activity, selectivity and stability of the enzyme catalyst when vinyl esters have been used as acyl donor groups instead of acids in the cascade reaction. The process has been implemented in continuous flow reactor by coupling two fixed bed reactors. One of them containing the Co catalyst and the other the immobilized lipase, obtaining an overall yield to the desired diester close to 90%, which has remained stable for 60 hours of operation.

Acknowledgments

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Experimental Section

Materials and chemicals

HMF (>97% purity) was obtained from Carbosynth. Lipase acrylic resin from Candida antarctica (Novozym 435), lipase from Pseudomonas fluorencens immobilized in Sol-Gel-AK and Lipase B from Candida antarctica immobilized in Sol-Gel-AK on pumice, glacial acetic acid, butyric acid, hexanoic acid and octanoic acid, $Co(NO_3)_2{\cdot}6H_2O$, NaOH, Na_2EDTA were purchased from Sigma Aldrich. Molecular sieves, 4A, 1-2 mm (0.04-0.08 in) beads was supplied by Alfa Aesar. 2-MTHF was obtained by Scharlau. Vinyl hexanoate was obtained from Tokio Chemical Industry. Nafion SAC-13 was purchased from Sigma Aldrich. MgO sample with crystallite size of 3 nm and 670 m^2g^{-1} surface area was purchased from NanoScale Materials and was calcined at 450 °C to remove absorbed impurities and carbonates before reaction.

Catalyst preparation

Preparation of Co@C catalyst

The Co@C catalyst was prepared according to the literature[16] following a combination of the hydrothermal synthesis method and *in situ* hydrogen reduction process. In general, a mixture of $Co(NO_3)_2{\cdot}6H_2O$ (6.98 g), Na_2EDTA (4.47 g), and

NaOH (0.96 g) was dissolved in 20 mL of deionized water. Then, 10 mL methanol were added to the aqueous solution under stirring at room temperature. After the homogeneous solution is formed, 23 mL of the mixture was transferred into a 35 mL stainless steel autoclave and sealed, followed by a static hydrothermal treatment at 200 °C for 24 h. The generated precipitate was filtered and washed first with deionized water and then with acetone several times. The obtained purple solid, denoted as Co-EDTA is further heat-treated and reduced with a rate of 10 °C/min and kept for 4 h at 450 °C in a 50 mL/min H_2 flow. After being cooled to room temperature in H_2 atmosphere, a magnetic black solid is obtained and labeled as Co@C catalyst. The ICP analysis shows that the amount of cobalt in the Co@C catalyst is ≥ 95 wt%.

Preparation of Co@C nanoparticles from the thermal decomposition of metal-organic framework (MOF) precursor

Co-BTC MOF was prepared following the reported procedure[17] using trimesic acid as a linker. In a typical synthesis, trimesic acid (1.05 g) and cobalt nitrate hexahydrate (2.91 g) were dissolved in a solvent composed by 20 mL of DMF, 20 mL of H_2O and 20 mL of ethanol under stirring at room temperature. Then, the solution was transferred to an autoclave and kept at 100 ˚C for 18 h. After that, Co-BTC-MOF was washed and dried at 60 ˚C. The thermal decomposition of Co-BTC-MOF in Ar at 600 ˚C yielded the Co-BTC sample. The sample was pre-reduced with H_2 at 160 ºC before the catalytic tests. The cobalt content of this sample is 30 wt%.

Preparation of Co@C/C catalyst

The supported Co@C/C catalyst was prepared according to the literature.[25] Cobalt (II) acetate tetrahydrate (127 mg) and 1,10-phenanthroline (184 mg)

(Co:phenanthroline = 1:2 M ratio) were dissolved in ethanol (50 mL) at room temperature. Then, carbon powder (690 mg) (VULCAN® XC72R, Cabot Corporation) was added and the whole mixture was refluxed for 4 h. The suspension was cooled to room temperature and the solvent was removed by evaporation. The solid obtained was dried at 60 ^{o}C for 12 h and then treated at 800 ^{o}C in a oven using a ramp rate of 25 ^{o}C/min, and held at 800 $^{\circ}$C for 2 h under Ar atmosphere. After that, the sample was cooled down to room temperature. The cobalt content of this sample is 3 wt %.

Characterization Techniques

The metal content in the samples and metal leaching were analyzed by inductively coupled plasma atomic emission spectroscopy (ICP-AES) using a Varian 715-ES.

Samples for electron microscopy studies were prepared by dropping the suspension of the powder sample using CH_2Cl_2 as the solvent directly onto holey-carbon coated copper grids. All the measurements were performed in a JEOL 2100F microscope operating at 200 kV both in transmission (TEM) and in scanning transmission modes (STEM). STEM images were obtained using a high angle annular dark-field detector (HAADF), which allows Z-contrast imaging.

Field emission scanning electron microscopy (FESEM) measurement was performed with a ZEISS Ultra 55 FESEM. The solid powder sample was adsorbed on conductive carbon tape.

Powder X-ray diffraction (XRD) were performed using a PAnalytical CubiX diffractometer using Cu Kα radiation and a multisampling handler.

Raman spectra were recorded at ambient temperature with a 785 nm HPNIR excitation laser on a Renishaw Raman spectrometer “Reflex” equipped with an

Olympus microscope and a CCD detector. The laser power on the sample was 15 mW and 20 acquisitions were taken for each spectrum.

General reaction procedures

Hydrogenation reaction of HMF

In a typical procedure, HMF (0.5 mmol), Co@C (10 mg), methanol (5 mL), and dodecane as internal standard were charged in a 13 mL stainless steel autoclave reactor with a Teflon vessel containing a magnetic stirring bar. Then, the reactor was sealed, and purged by flushing three times with 10 bar of hydrogen and then pressurized with 10 bar of H_2 and heated at 110 ^oC while stirring at 950 rpm. After reaction the catalyst was removed with a magnet and the products were analyzed by GC (Varian CP 3800) equipped with a DB-wax capillary column and a FID detector. The products were identified by GC-MS (Agilent 6890N). The molar balance was checked in each tests and accounted >97 %.

Esterification of BHMF with hexanoic acid in the presence of Nafion SAC-13

A 10 mL two-necked round bottom flask with a water-cooled condenser was charged with of BHMF (0.5 mmol, 64 mg), hexanoic acid (2 mmol, 232 mg), 5 mL of 2-MTHF as solvent, 13 mg of Nafion SAC-13 (previously dried at 100 ^oC under vacuum), and dodecane as internal standard. The mixture was refluxed for the required temperature (80 ^oC) under stirring at 1000 rpm. Samples were taken at regular intervals and analyzed by GC.

Transesterification reaction between BHMF and hexanoic acid methyl ester

The reaction was performed in a 10 mL two-necked round bottom flask. BHMF (1 mmol, 128 mg), methyl hexanoate (4 mmol, 520 mg), and the nanocrystalline

MgO catalyst (25.6 mg) were added to the flask, and subsequently the reaction mixture was heated at 120 °C in a silicone bath fitted with a magnetic stirrer and a temperature controller. The progress of the reaction was followed by taking samples at regular times that were then analyzed by GC using dodecane as external standard.

One-pot synthesis of of 2,5-bis(acetoxymethyl)furan

To a 13 mL autoclave with Teflon vessel were added 5-hydroxymethylfurfural (63 mg, 0.5 mmol), Co@C NPs (30 mg), dodecane (20 mg), and 2-MTHF (5 mL). The autoclave was sealed and purged with H_2 three times, pressurized with 10 bar of H_2 and heated at 110 °C while stirring at 950 rpm. After 10 reaction, the autoclave was cooled and the Co@C catalyst was remvoved with a magnet. Then, to the solution of BHMF, dry pyridine (0.89 mL, 870 mg), and acetic anhydride (0.11 mL, 1.16 mmol, 2.5 eq.) were added dropwise. The reaction mixture was stirred at 24 °C for 24 h. The products were analyzed by GC and GC-MS.

Enzymatic esterification of BHMF

In a 3 mL glass batch reactor, a solution of 2,5-bis(hydroxymethyl)furan (0.05 mmol, 6.4 mg) in 2-MTHF (1 mL), carboxylic acid (0.2 mmol), molecular sieves (200 mg), and the biocatalyst Novozym 435 (25 mg) were placed. The reactor was sealed and the reaction mixture was stirred (800 rpm) at 35 °C for 24 h. Samples (25 µL) were taken from the reaction mixture at different times, dissolved in ethanol, and analyzed by GC (Varian CP-3800) equipped with a capillary column (DB-wax, 15mx0.32mmx0.25µm). The molar balance was confirmed to be higher than 96%.

One-pot reaction in batch reactor

HMF (0.5 mmol), Co@C (10 mg), 2-MTHF (5 mL), were charged in a 13 mL stainless steel autoclave reactor. Then, the reactor was purged by flushing hydrogen and then pressurized with 10 bar of H_2. After 10 h reaction time, the heterogeneous catalyst was removed with a magnet, and a solution of acyl donor (2 mmol), lipase Novozym 435 (250 mg), and molecular sieves (1 g) were added to the reactor while the temperature was kept at 35 ^oC during the required time. After that, the products were analyzed by GC and GC-MS.

To perform the recycling studies, after the reaction the organic phase was separated by filtration. The biocatalyst Novozym 435 was separated from the molecular sieves using an appropriated strainer, washed several times with 2-MTHF, dried and then reused directly in a second cycle**.**

Reduction of HMF in a fixed bed continuous flow reactor

The hydrogenation reaction of HMF with Co@C in a continuous fixed-bed reactor was performed in a tubular stainless-steel reactor. In a typical experiment, the reduced Co@C (0.335 g) was pelletized and sieved to a particle size of 0.2–0.4 mm, diluted with silicon carbide and placed in the flow reactor (0.65 cm external diameter). Before the reaction, the Co@C catalyst was reduced at 170 ^oC, 10 bar H_2, under a flow of H_2/N_2 (80/20) (50 mL min^{-1}) for 2 h. After that, the reactor was heated at 90 ^oC (the temperature was measured by using a thermocouple in direct contact with the catalytic bed), and a solution of HMF in MeOH (1.5 wt%) was fed by using a Gilson 305 HPLC pump at a rate of 12 mL h^{-1},(which corresponds to a weight hourly space velocity (WHSV) of 0.44 h^{-1} or a contact time of 2.27 h) together with a H_2/N_2 (80/20) flow (50 mL min^{-1}) at 10 bar. The product was accumulated at low temperature and analyzed offline by gas chromatography

using dodecane as an external standard and GC–MS. The mass balance was >97 %.

Synthesis of BHMF diesters in a fixed bed continuous flow reactor

The esterification of BHMF with vinyl hexanoate using Lipase (Novozyme 435) in a continuous fixed bed reactor was performed in a tubular stainless reactor (1 mm inner diameter, 35 mm long). In a typical experiment Novozym 435 (0.33 g) was diluted with molecular sieves 4A (1.8 g) and packed in a stainless reactor coupled with an electric heater controller that maintain constant temperature (35 °C). The reactor was fed with a solution of BHMF in 2-MTHF (1.5 wt%) and vinyl hexanoate (6.5 wt%) by using a Gilson 305 HPLC Pump at a rate of 12 mL h^{-1}, which corresponds to a weight hourly space velocity (WHSV) of 0.48 h^{-1} or a contact time of 2.1 h. Samples were withdrawn at regular times and the reaction products analyzed by GC and GC-MS using dodecane as an external standard. Products were characterized by ^{1}H-RMN, ^{13}C-RMN and GC-MS.

Spectral data

2,5-Bis(hydroxymethyl)furan diacetate**:** ^{1}H NMR (300 MHz, CD_3OD) δ 6.41 (s, 2H), 5.03 (s, 4H), 2.05 (s, 6H); ^{13}C NMR (75 MHz, CD_3OD δ 172.25, 151.84, 112.44, 58.98, 20.64; EIMS (70 eV) m/z (%) 212 $[M]^+$ (2), 153 (33), 110 (100), 43 (38).

Butanoic acid, 1,1'-[2,5-furandiylbis(methylene)] ester**:** ^{1}H NMR (300 MHz, CD_3OD) δ 6.41 (s, 2H), 5.04 (s, 4H), 2.31 (t, *J* = 7.3 Hz, 4H), 1.67–1.59 (m, 4H), 0.93 (t, *J* = 7.4 Hz, 6H); ^{13}C NMR (75 MHz, CD_3OD) δ 174.73, 151.92, 112.33, 58.79, 36.76, 19.40, 13.81; EIMS (70 eV) m/z (%) 268 $[M]^+$ (1), 181 (40), 110 (100), 71 (61).

Hexanoic acid, 1,1'-[2,5-furandiylbis(methylene)] ester**:** ^{1}H NMR (300 MHz, CD_3OD) δ 6.41 (s, 2H), 5.04 (s, 4H), 2.33 (t, *J* = 7.4 Hz, 4H), 1.63–1.56 (m, 4H), 1.31–1.28 (m, 8H), 0.90 (t, *J* = 6.8 Hz, 6H); ^{13}C NMR (75 MHz, CD_3OD) δ 174.88, 151.91, 112.37, 58.80, 34.85, 32.31, 25.69, 23.35, 14.24; EIMS (70 eV) m/z (%) 324 $[M]^+$ (1), 209 (37), 110 (100), 99 (62).

Octanoic acid, 1,1'-[2,5-furandiylbis(methylene)] ester: ^{1}H NMR (300 MHz, CD_3OD) δ 6.41 (s, 2H), 5.04 (s, 4H), 2.33 (t, *J* = 7.4 Hz, 4H), 1.63–1.58 (m, 4H), 1.33–1.27 (m, 16H), 0.90 (t, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, CD_3OD) δ 174.88, 151.91, 112.36, 58.80, 34.89, 32.84, 30.05, 26.01, 23.64, 14.40; EIMS (70 eV) m/z (%) 380 $[M]^+$ (1), 127 (55), 110 (100), 57 (33).

(5-(hydroxymethyl)furan-2-yl)methyl acetate: EIMS (70 eV) m/z (%) 170 $[M]^+$ (5), 110 (100), 79 (45), 43 (62).

(5-(hydroxymethyl)furan-2-yl)methyl butyrate: EIMS (70 eV) m/z (%) 198 $[M]^+$ (2), 111 (100), 71 (49), 43 (51).

(5-(hydroxymethyl)furan-2-yl)methyl hexanoate: EIMS (70 eV) m/z (%) 226 $[M]^+$ (2), 111 (100), 99 (51), 43 (43).

(5-(hydroxymethyl)furan-2-yl)methyl octanoate: EIMS (70 eV) m/z (%) 254 $[M]^+$ (1),127(48), 111 (100), 57 (74).

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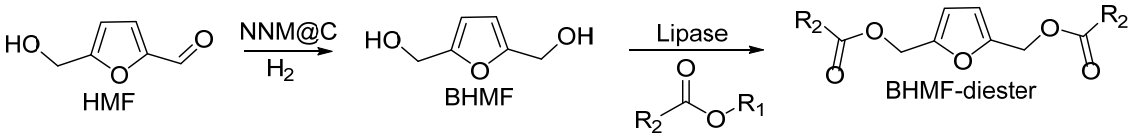
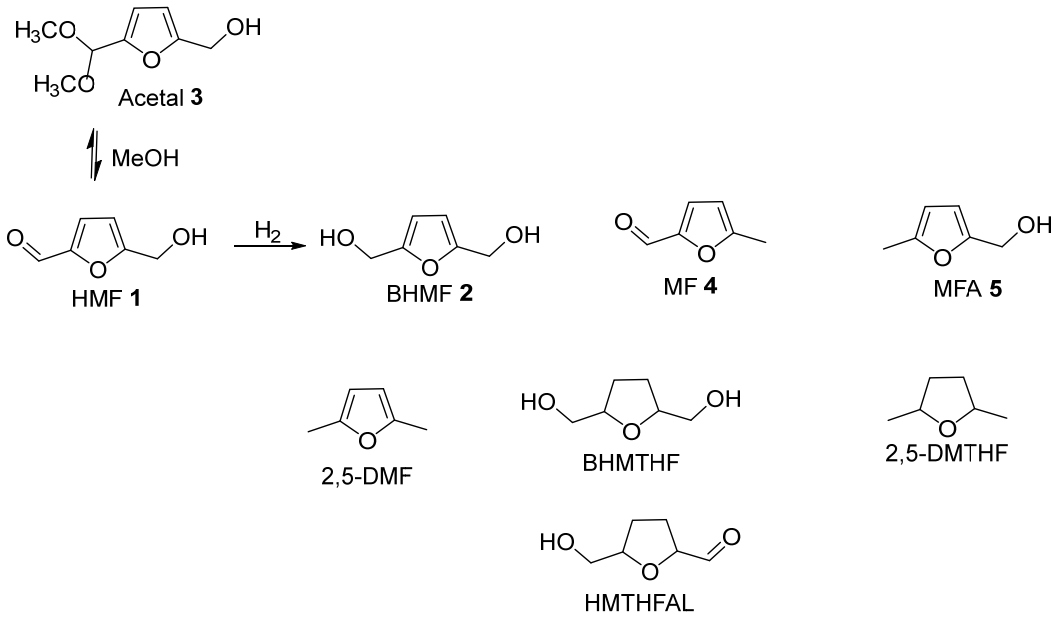
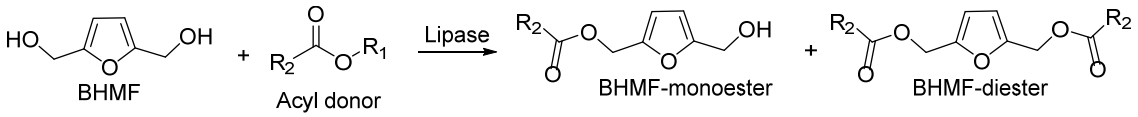


Scheme 1. Cascade Process for the production of plasticizers from HMF.



Scheme 2. Possible compounds formed in the reduction reaction of HMF.



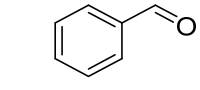
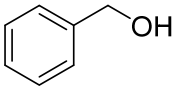
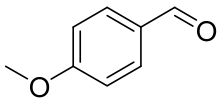
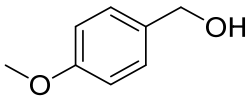
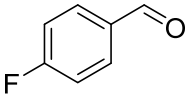
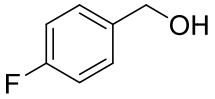
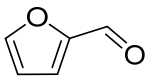
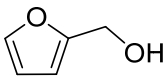
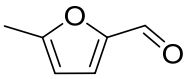
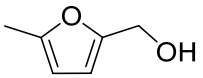
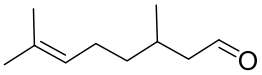
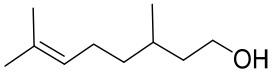
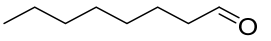
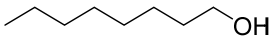
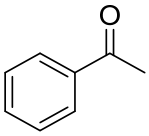
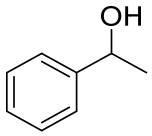
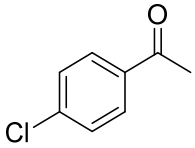
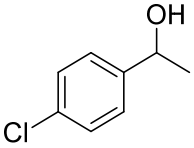
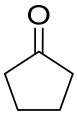
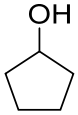
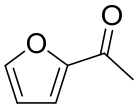
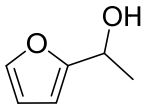
Scheme 3. Esterification reaction of BHMF using lipase (Novozym 435).

Table 1. Hydrogenation of HMF using different non-noble catalysts.[a]

Entry	Catalysts	Time (h)	Conv. (%)	Yield (%)		Select. (%)
				2	**3**	**2**
1[b]	Co@C	2	90[e]	89	-	99
		6	98[e]	98	-	99
2[c]	Co@C	2	93	93	<1	99
		3	99	99	<1	99
3	Co@C	2	97[e]	96	-	99
		6	99[e]	96	-	97
4[d]	Co@C	2	24	23	<1	96
		6	72	71	<1	99
		24	91	90	1	99
5	Co@C-250a	2	50	50	-	100
		6	93	92	1	99
6	Co@C-450a	2	15	15	-	100
		6	29	27	2	93
		24	77	70	7	91
7	Co_3O_4-R	2	21	19	2	90
		6	49	47	2	96
		24	84	82	2	98
8	Co-BTC	2	12	4	8	33
		24	58	32	26	55
9	Co@C/C	2	10	4	6	40
		24	55	38	17	69
10	-	6	8	3	5	37
		24	15	8	7	53

[a] Reaction conditions: HMF (0.5 mmol, 63 mg), substrate/Co molar ratio of 3.1, 110 °C, 10 bar H_2, in MeOH 5 mL. [b] At 90 °C, 20 bar H_2; [c] at 110 °C, 20 bar H_2; [d] at 120 °C, 5 bar H_2. [e] Compounds **4** and **5** were detected in minor amounts.

Table 2. Results of hydrogenation of different carbonyl compounds using Co@C as catalyst.[a]

Entry	Substrate	Product	Time (h)	Conv. (%)	Yield (%)	Select. (%)
1			2 3	96 99	96 99	100 100
2[b]			3	99	95	96
3[b]			4	99	98	99
4			2	99	99	100
5			4 6	97 100	97 100	100 100
6			2	98	98	100
7			3 6	97 99	97 99	100 100
8[c]			4 7	91 99	91 99	100 100
9[c]			8 20	82 91	82 91	100 100
10[c]			3 6	90 99	90 99	100 100
11[c]			6 2	62 82	62 82	100 100

[a]Reaction conditions: carbonyl compound (0.5 mmol), Co@C (10 mg) (substrate/Co molar ratio of 3.1), 110 °C, 10 bar H_2, in MeOH (5 mL). Yields and conversions determined by GC using dodecane as an internal standard. [b] The corresponding dimethyl acetal was detected as by-product. [c] Reactions carried out with 40 mg of catalyst.

Table 3. Influence of solvent in the hydrogenation of HMF with Co@C catalyst.[a]

Entry	Solvent	Conv. (%)	Yield (%)			Select. **2** %
			2	**4**	**5**	
1	MeOH	97	95	1	1	98
2	Isopropanol	98	86	2	10	88
3[b]	Acetone	19	13	-	-	60
4[c]	2-MTHF	30	26	2	2	87
5[d]	2-MTHF	95	91	-	4	96

[a]Reaction conditions: HMF (0.5 mmol, 63 mg), 10 mg Co@C, solvent (5 mL), 110 ^{o}C, 10 bar H_2, 2 h. [b] 6% of a product coming from acetone and HMF aldol condensation was detected (6 h). [c] at 10 h; [d] using 30 mg Co@C at 10 h.

Table 4. Results of yields and selectivities of the BHMF diesters obtained through the one-pot chemoenzymatic process using different acyl donors.

First step				Second step					Chemoenzymatic process	
Entry	Conv. (%)	Yield **2** (%)	Select. **2** (%)	Acyl donor	T (h)	Conv. (%)	Yield (%)	Select. (%)	Total Yield (%)	Total Selectivity (%)
1	96	92	96	CH_3COOH	24	93	47	50	43	45
2	95	91	96	$CH_3(CH_2)_2COOH$	24	94	94	100	85	90
3	95	92	97	$CH_3(CH_2)_4COOH$	11	99	99	100	91	96
4	96	93	97	$CH_3(CH_2)_6COOH$	24	99	99	100	92	96
5	97	92	95	$CH_3(CH_2)_4COOC_2H_3$	0.5	97	97	100	89	92

Reaction conditions: First step HMF (0.5 mmol, 63 mg), Co@C (30 mg), 2-MTHF (5 mL) 110 ^oC, 10 bar H_2, 10 h. Second step: molar ratio BHMF/acyl donor (1/4), Novozym 435 (250 mg), molecular sieves (1 g), at 35 ^oC.

Table 5. Reusability of the catalysts in the chemoenzymatic cascade process.

	First step				Second step				Chemoenzymatic process	
Cycle	Time (h)	Conv. (%)	Yield **2** (%)	Select. **2** (%)	Time (h)	Conv. **2** (%)	Yield (%) BHMF diester	Select. (%) BHMF diester	Total Yield (%)	Total Selectivity (%)
1	9	95	91	96	11	98	96	98	87	92
2	10	94	90	95	15	98	93	95	84	89
3	12	91	87	96	20	96	77	80	67	74

Reaction conditions: First step HMF (0.5 mmol, 63 mg), Co@C (30 mg,) 2-MTHF (5 mL) 110 ^{o}C, 10 bar H_2. Second step: molar ratio BHMF/hexanoic acid (1/4), Novozym 435 (250 mg), molecular sieves (1g) at 35 ^{o}C.

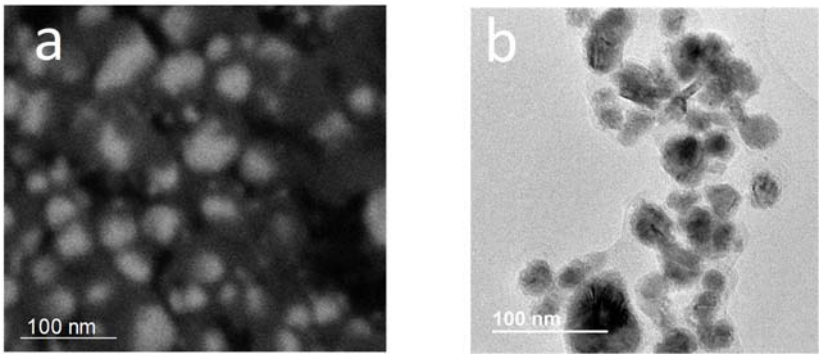


Figure 1. (a) FESEM image of Co@C sample obtained by ESB detector. (b) TEM image of Co@C sample.

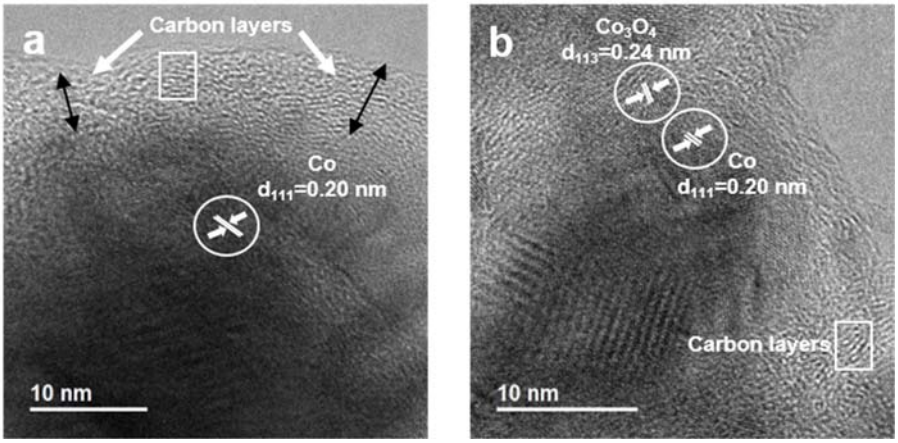


Figure 2. (a) HRTEM image of a single Co nanoparticle covered by thin carbon layers. (b) HRTEM image of surface structures of Co nanoparticle covered by thin carbon layers. The lattice of Co_3O_4 can be observed on the outer surface layer of Co@C nanoparticle.

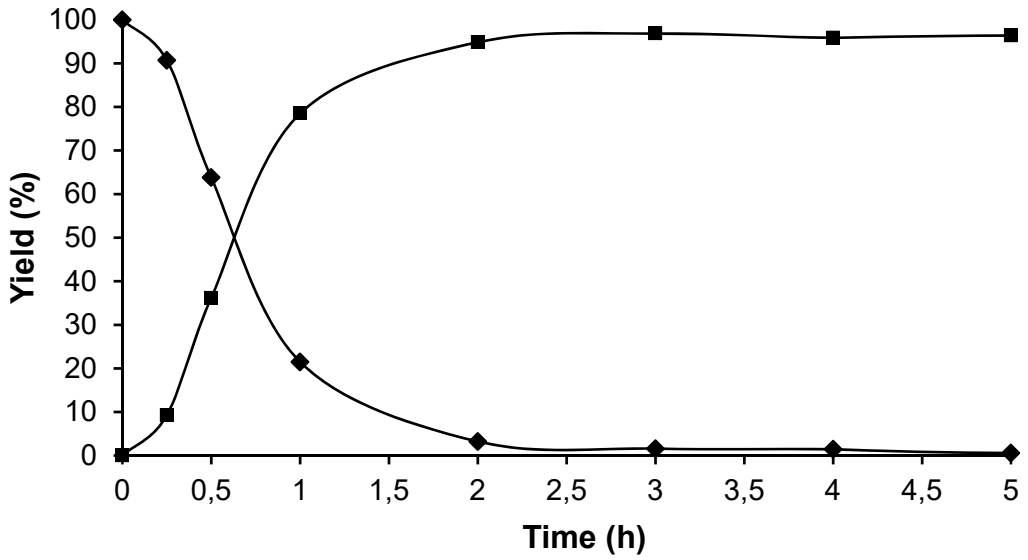


Figure 3. Kinetic of reduction of HMF using Co@C catalyst. Reaction conditions: 0.5 mmol HMF, 10 mg of catalyst, 5 mL methanol, 110 ºC and 10 bar of H_2. HMF (♦), BHMF (■).

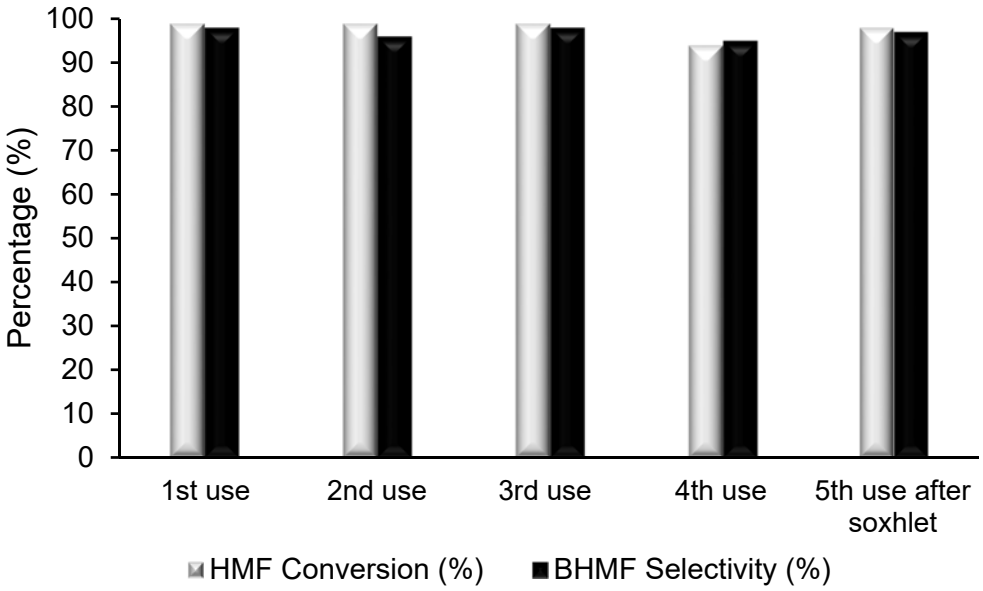


Figure 4. Reuses of Co@C catalyst in the hydrogenation of HMF to BHMF by catalyst and the stability test. Reaction conditions: 0.5 mmol HMF, 10 mg of Co@C, 5 mL methanol as solvent, 110 °C, 10 bar of H_2 at 4 h of reaction. First use at 2 h.

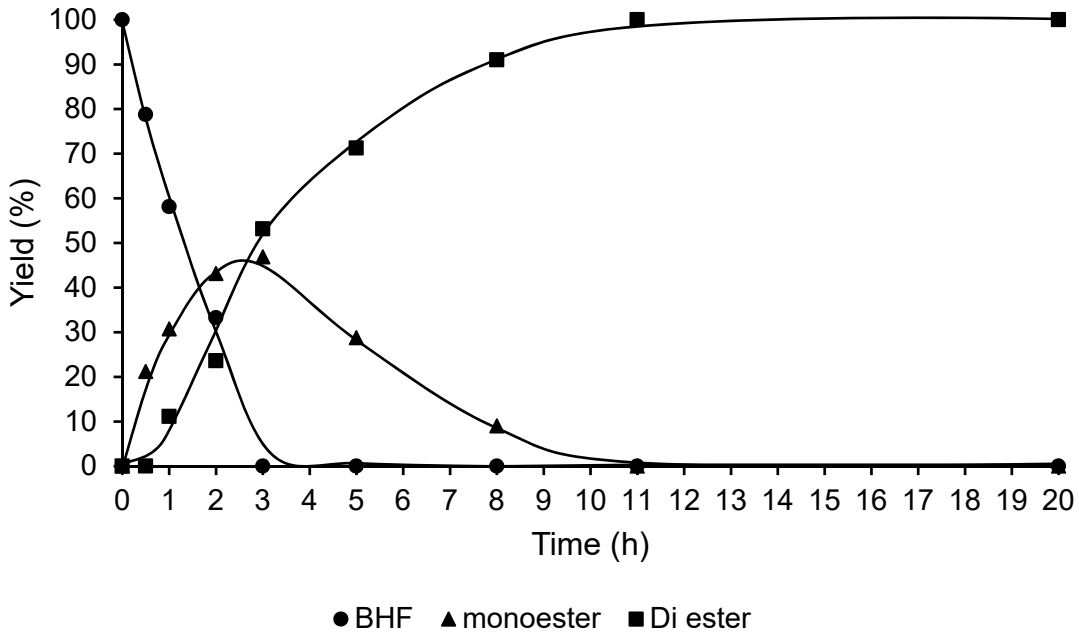


Figure 5. Kinetic curve of esterification of BHMF (0.05 mmol) with hexanoic acid (0.2 mmol), using Novozym 435 (25 mg) in MTHF (1 mL), and molecular sieves (200 mg) at 35 ºC. BHMF (●), BHMF Monoester (▲) and BHMF Diester (■).

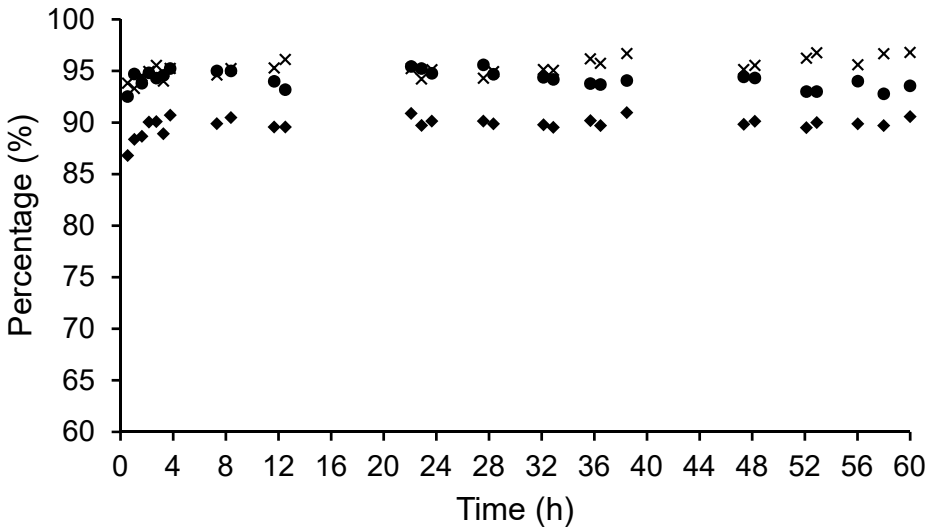


Figure 6. Results of the hydrogenation reaction of HMF in a continuous-flow reactor using Co@C catalyst. (Reaction conditions: HMF in MeOH feed (1.5 wt%), flow rate 12 mL h^{-1} (WHSV: 0.44 h^{-1}) at 90 °C and 10 bar H_2). HMF Conversion (●), BHMF Yield (♦), BHMF Selectivity (×).

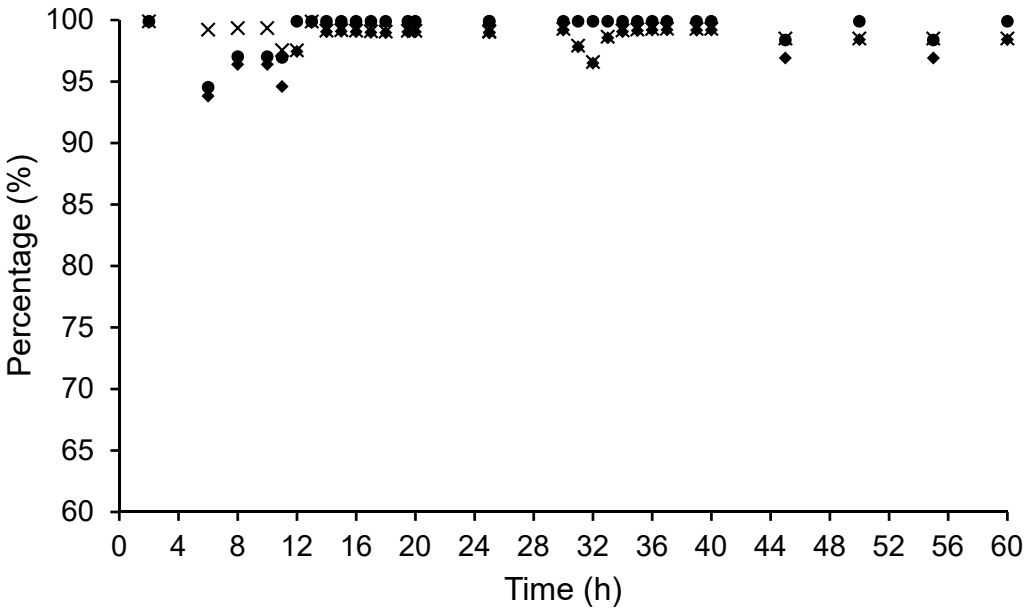


Figure 7. Results of the esterification of BHMF with vinyl hexanoate in a continuous-flow reactor using Novozym 435 as catalyst. Reaction conditions: BHMF in 2-MTHF feed (1.5 wt %) vinyl hexanoate (6.5 wt %), Novozym 435 (0.330 g), flow rate 12 mL h^{-1} (WHSV: 0.48 h^{-1}) at 35 °C. BHMF Conversion % (●), BHMF diester Yield % (♦), BHMF diester Selectivity % (×).

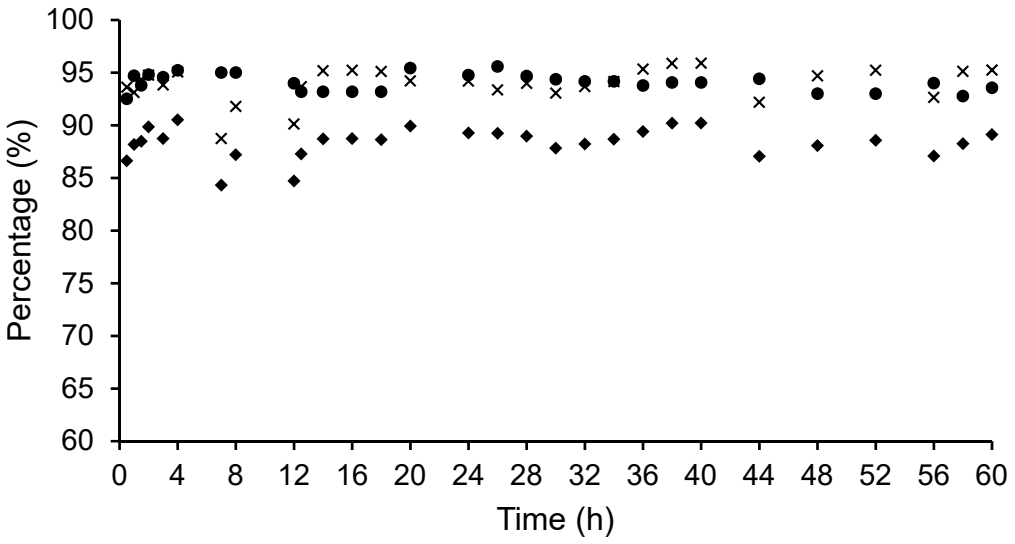


Figure 8. Results of the chemoenzymatic cascade process in a two consecutive continuous-flow reactors. HMF Conversion (•), Total Yield to BHMF diester (♦), Total Selectivity to BHMF diester (x).

Supporting Information

Chemoenzymatic synthesis of 5-Hydroxymethylfurfural (HMF) derived plasticizers by coupling HMF reduction with enzymatic esterification

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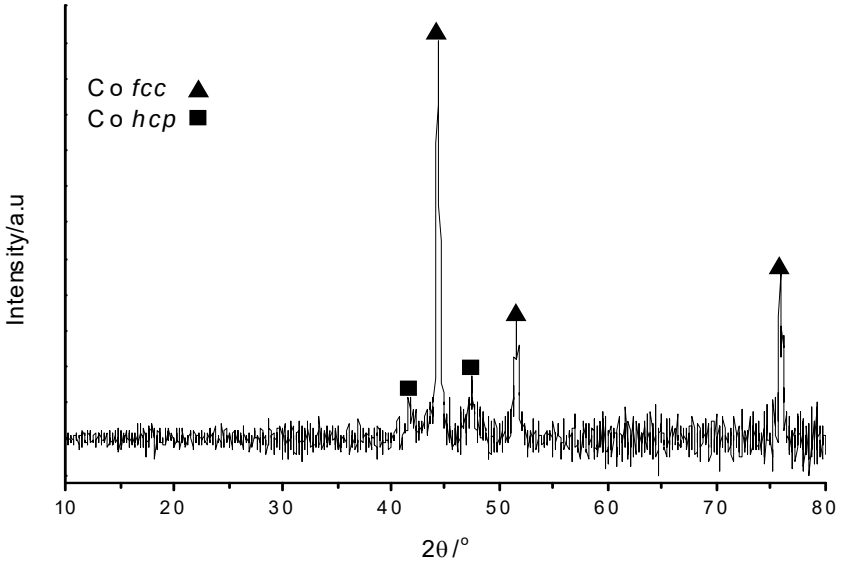

Figure S1. XRD patterns of Co@C catalyst: (▲) face-centered cubic phase (*fcc*), (■) hexagonal close-packed (*hcp*).

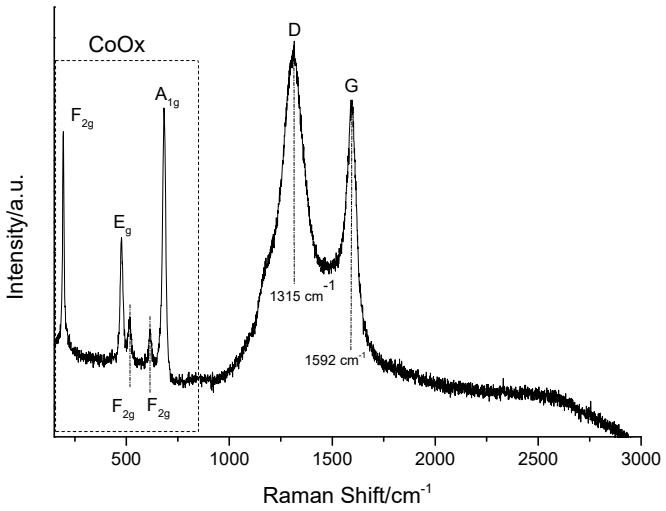

Figure S2. Raman spectra of Co@C. Raman bands corresponding of Co_3O_4 (F_{2g}, E_g, and A_{1g}) and typical Raman signals of layered carbon, bands at 1315 cm^{-1} and 1592 cm^{-1}, which corresponding to the D and G bands, respectively, and disordered carbon can be observed.

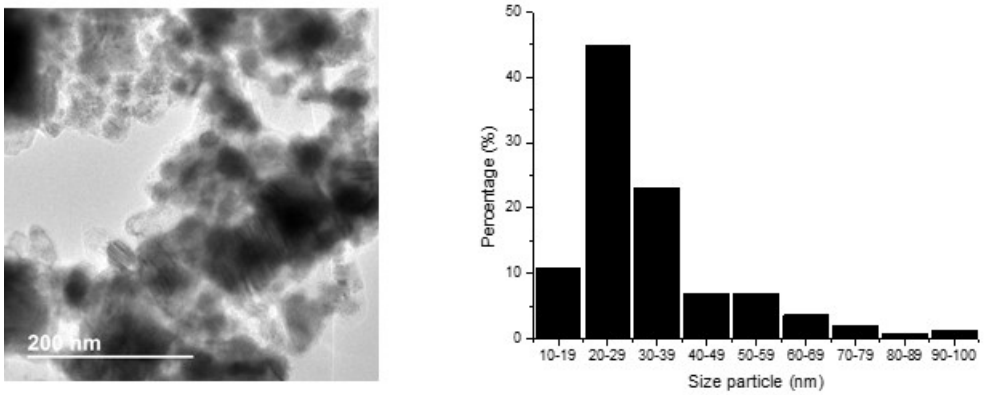

Figure S3. TEM image of Co@C catalyst and size distribution of Co nanoparticles in the Co@C sample.

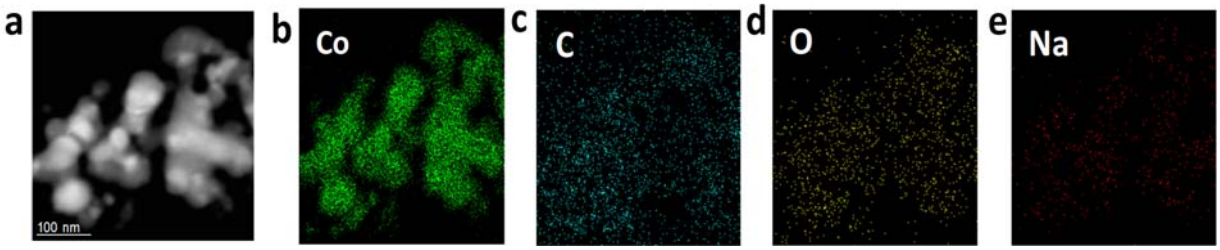

Figure S4. (a) STEM-HADDF image of Co@C nanoparticles. (b-e) Elemental mapping of Co, C, O and Na in the Co@C catalyst

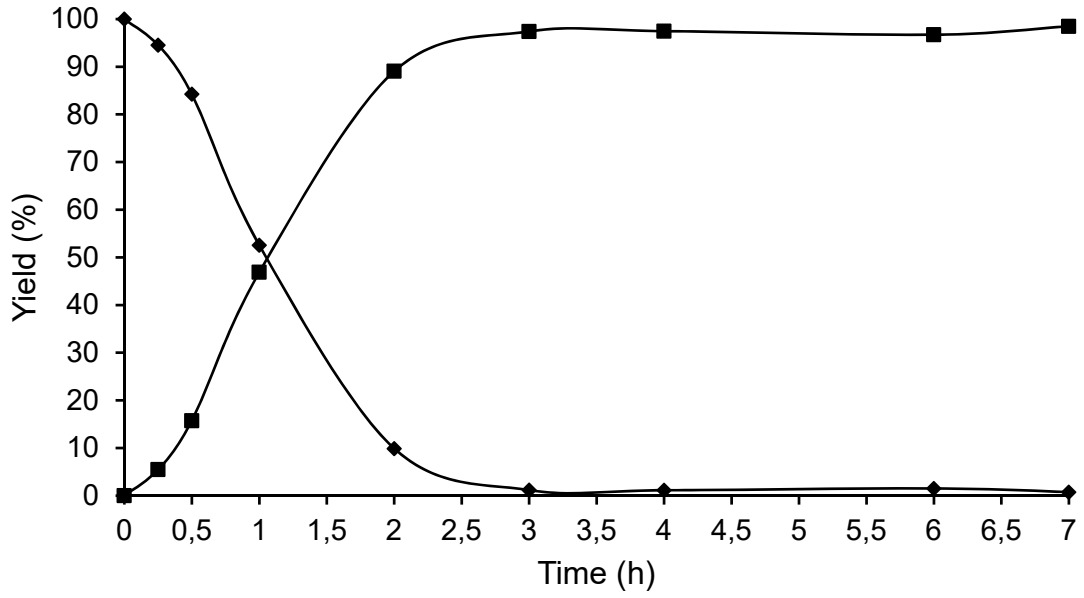

Figure S5. Reduction of HMF into BHMF using Co@C catalyst. Reaction conditions: 0.5 mmol HMF, 10 mg catalyst, 5 mL methanol as solvent, 90 ºC and 20 bar of H_2. HMF (♦), BHMF (■).

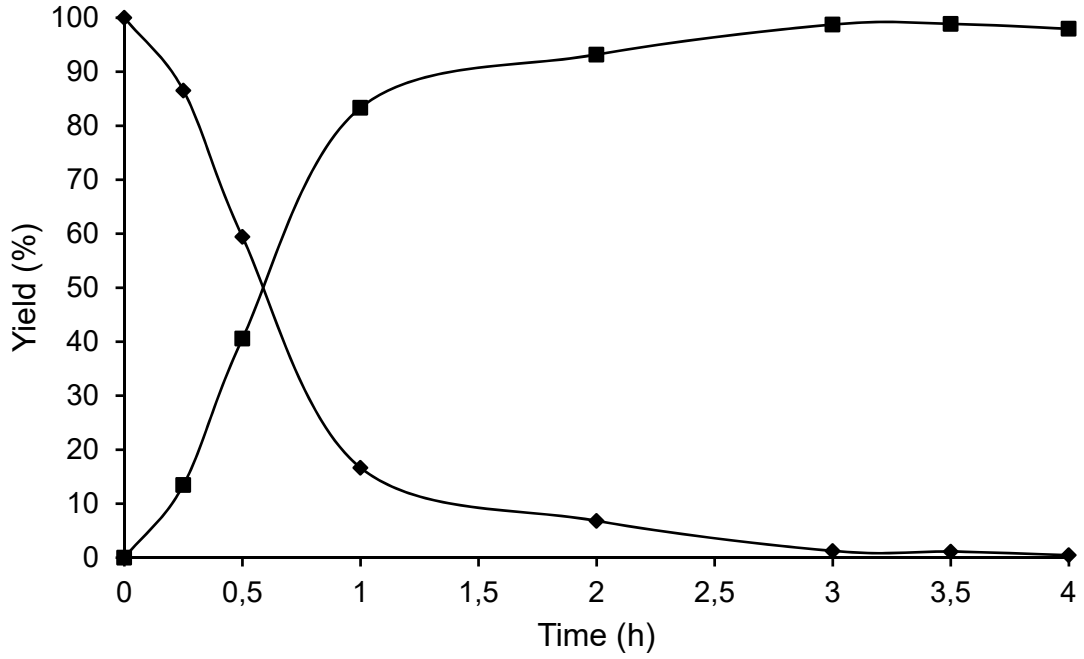

Figure S6. Reduction of HMF with Co@C catalyst. Reaction conditions: 0.5 mmol HMF, 10 mg catalyst, 5 mL methanol, 110 ºC and 20 bar of H_2. HMF (♦), BHMF (■).

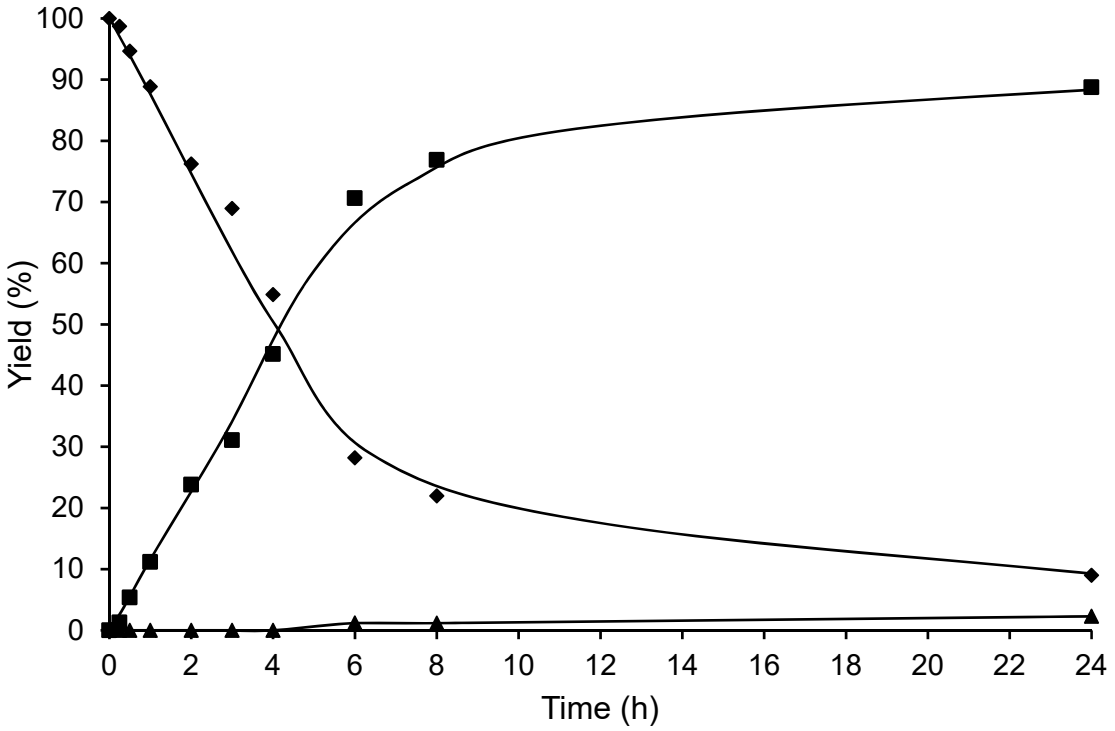

Figure S7. Reduction of HMF with Co@C catalyst. Reaction conditions: 0.5 mmol HMF, 10 mg catalyst, 5 mL methanol, 120 ºC and 5 bar of H_2. HMF (♦), BHMF (■), **3** (▲).

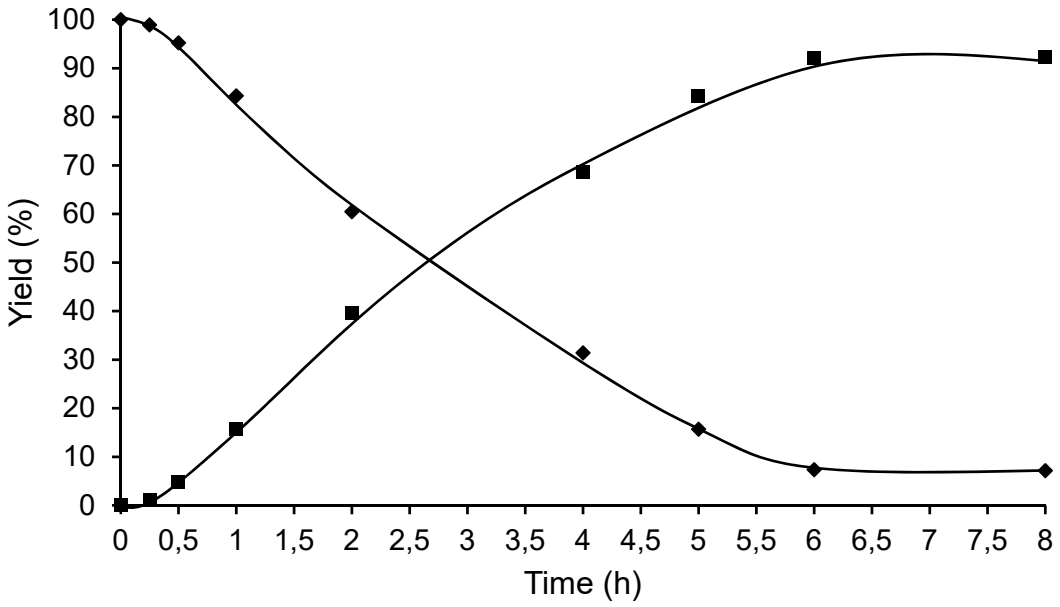

Figure S8. Reduction of HMF with Co@C-250a catalyst. Reaction conditions: 0.5 mmol HMF, 10 mg Co@C-250a as the catalyst, 5 mL methanol as solvent, 110 ºC and 10 bar of H_2. HMF (♦), BHMF (■).

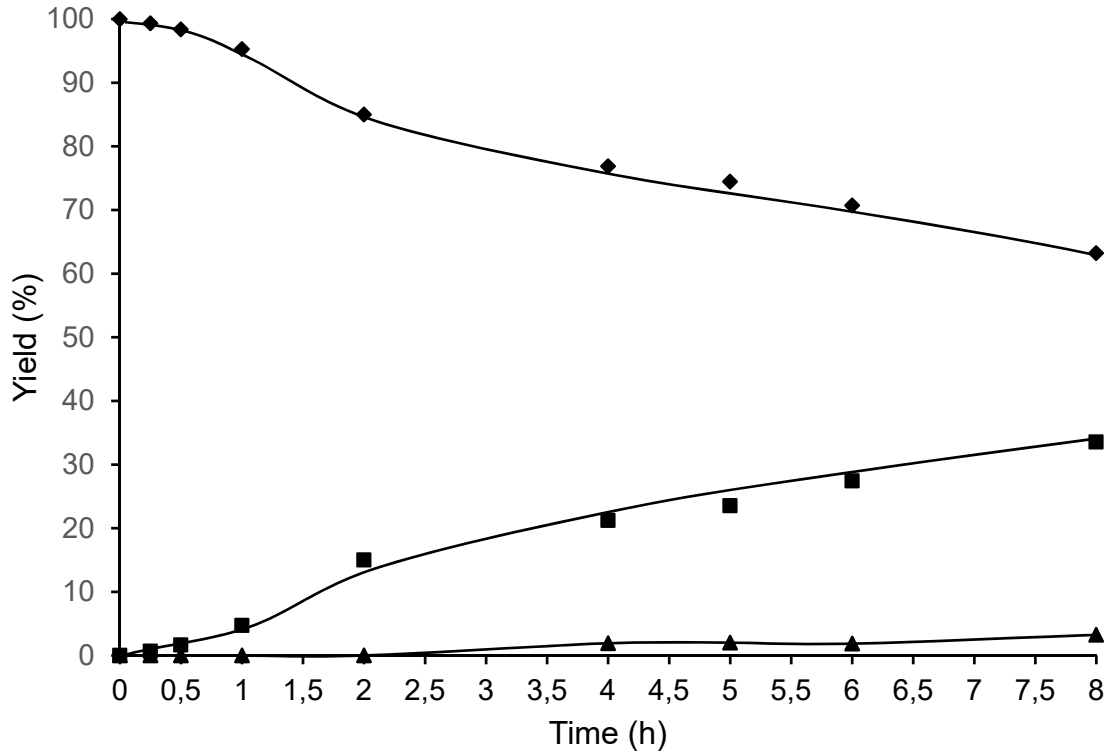

Figure S9. Reduction of HMF with Co@C-450a. Reaction conditions: 0.5 mmol HMF, 10 mg Co@C-450a as the catalyst, 5 mL methanol as solvent, 110 ºC and 10 bar of H_2. HMF (♦), BHMF (■), **3** (▲).

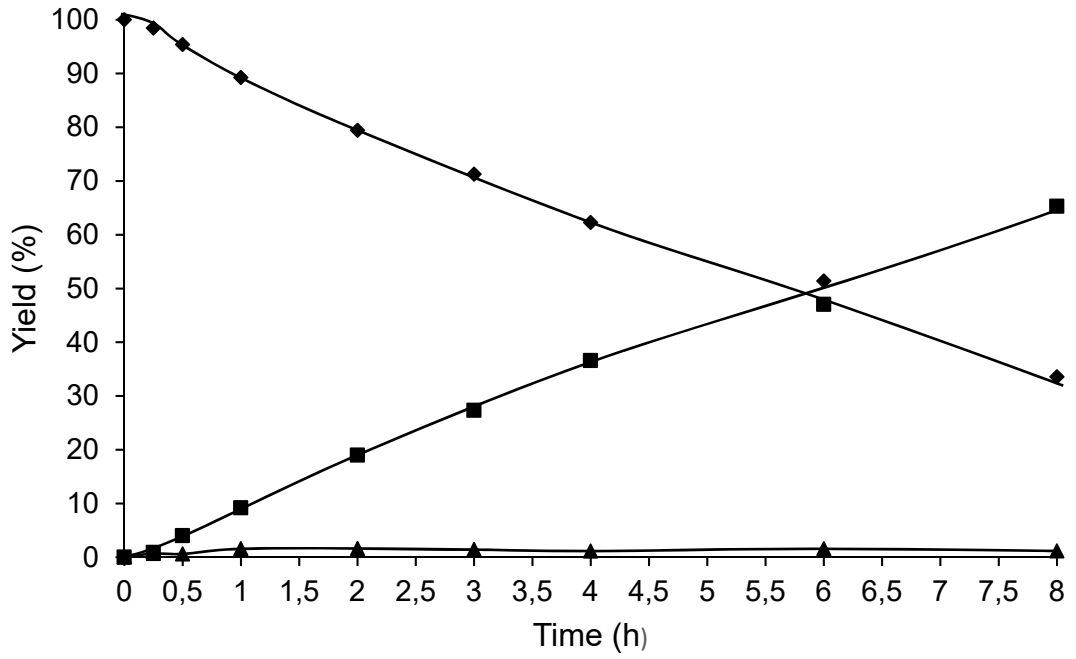

Figure S10. Reduction of HMF with Co_3O_4-R. Reaction conditions: 0.5 mmol HMF, 10 mg Co_3O_4-R as the catalyst, 5 mL methanol as solvent, 110 ºC and 10 bar of H_2. HMF (♦), BHMF (■),**3** (▲).

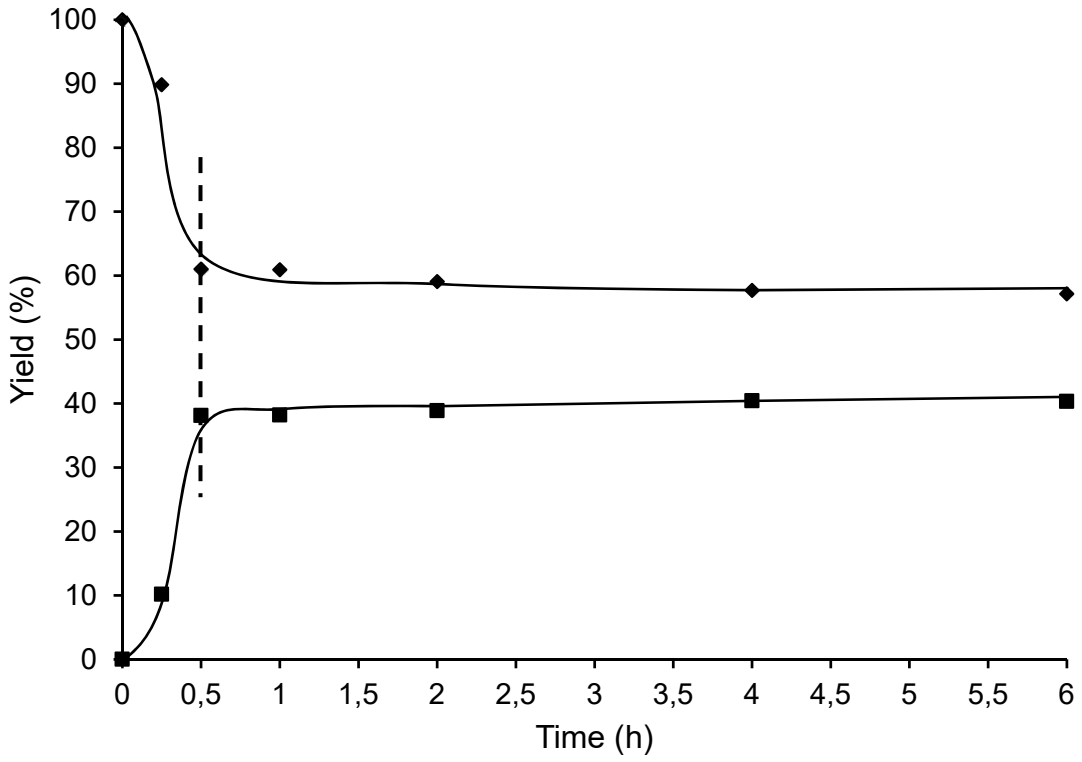

Figure S11. Leaching test with catalyst removal during the reaction course. Reaction conditions: 0.5 mmol HMF, 10 mg Co@C as the catalyst, 5 mL methanol as solvent, 110 ºC and 10 bar of H_2. After 0.5 h, the catalyst was separated and the reaction was continued. HMF (♦), BHMF (■).

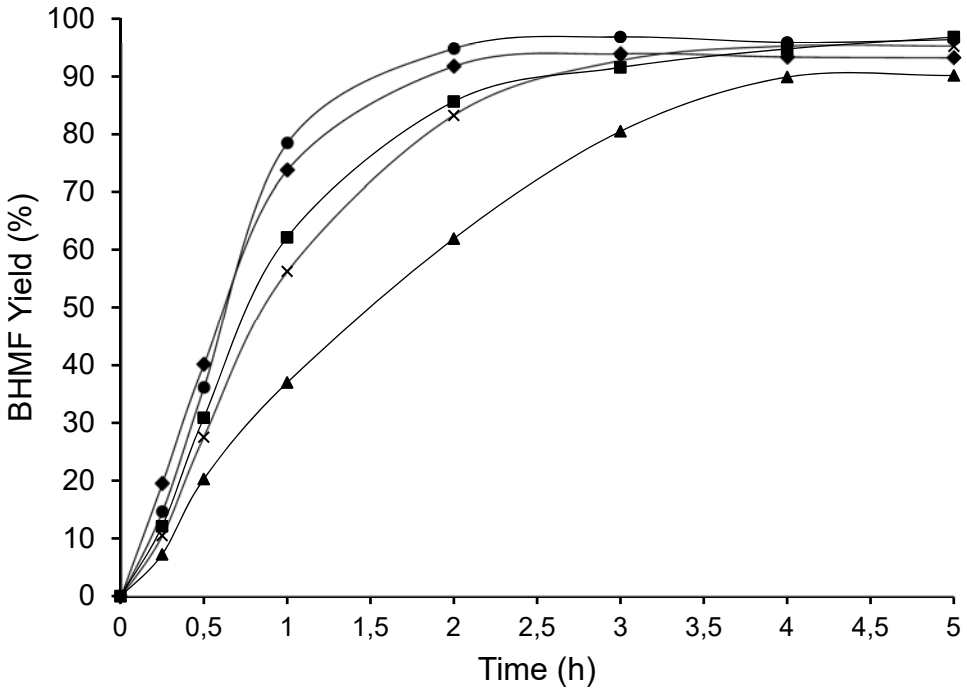

Figure S12. The catalytic performances of recycled Co@C NPs in reduction of HMF. Reaction conditions: 0.5 mmol HMF, 10 mg catalyst, 5 mL methanol as solvent, 110 ºC and 10 bar of H_2. First use (●), second use (♦), third use (×), fourth use (▲), fifth use after soxhlet (■).

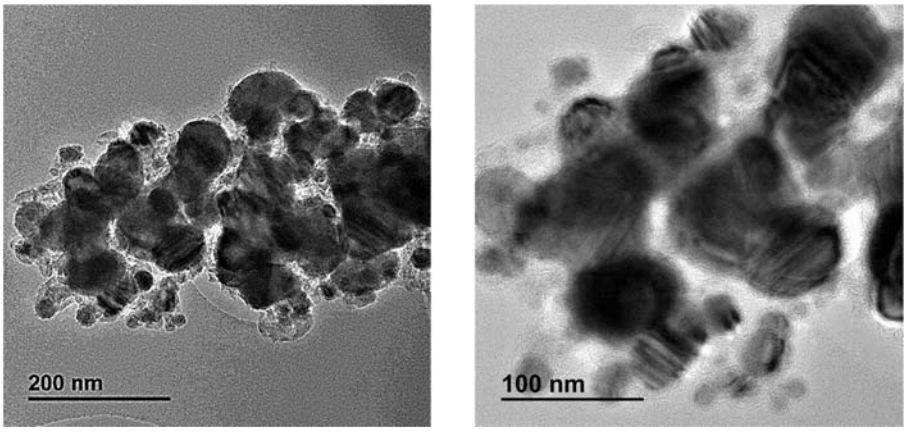

Figure S13. TEM images of Co@C catalyst after the fourth cycle in the hydrogenation reaction of HMF.

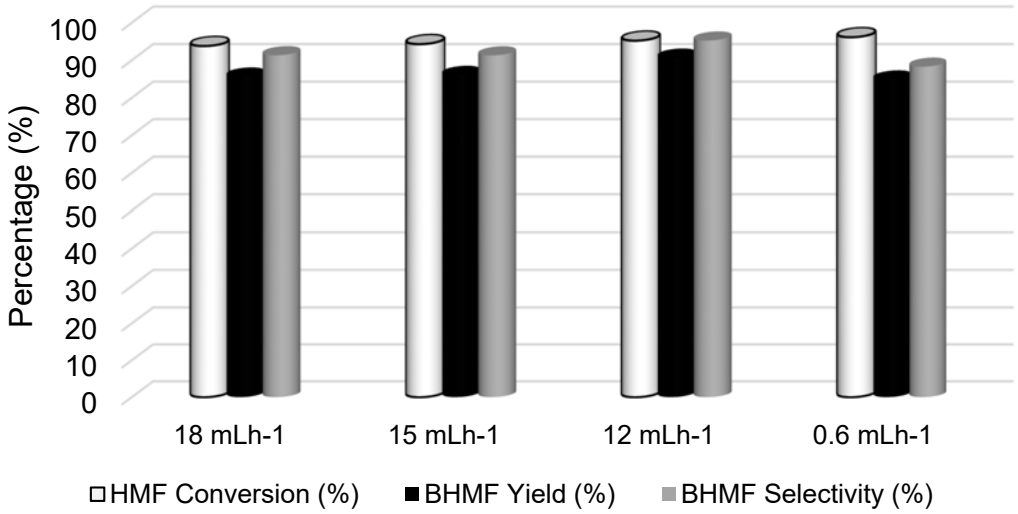

Figure S14. Optimization of flow rate in the hydrogenation of HMF in a continuous flow reactor. (Reaction conditions: HMF in MeOH feed (1.5 wt%), temperature: 90 °C, catalyst mass: 0.335 g, 10 bar H_2). Flow rate: 18 mLh^{-1} (WHSV 0.66 h^{-1}, contact time 1.52 h), 15 mLh^{-1} (WHSV 0.55 h^{-1}, contact time 1.82 h), 12 mLh^{-1} (WHSV 0.44 h^{-1}, contact time 2.27 h), 6 mLh^{-1} (WHSV 0.22 h^{-1}, contact time 4.55 h).

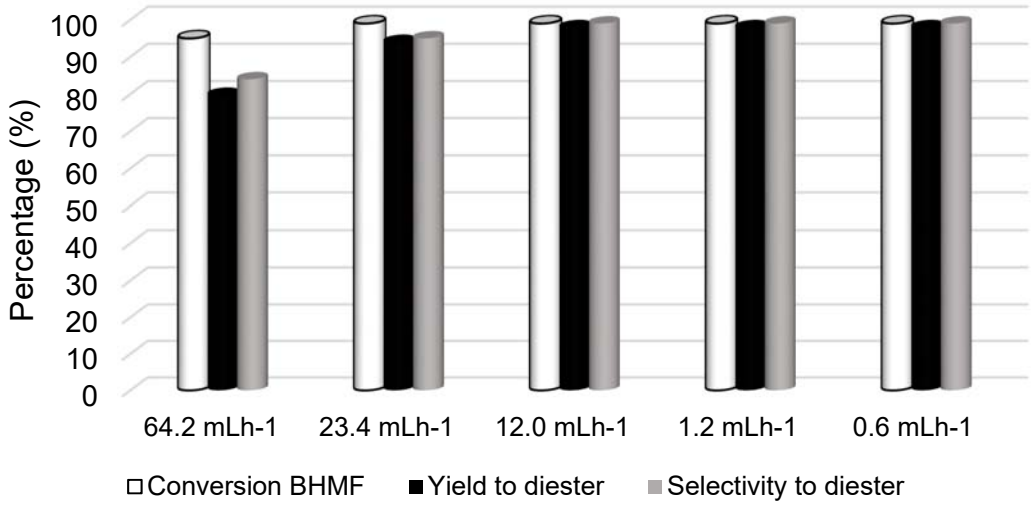

Figure S15. Optimization of flow rate in transesterification of BHMF with vinyl hexanoate in a continuous flow reactor. (Reaction conditions: feed: BHMF (1,5 wt%), and vinyl hexanoate (6.5 wt%) in 2-MTHF, temperature: 35 °C, catalyst mass: 0.330 g,). Flow rate: 64 mLh^{-1} (WHSV 2.5 h^{-1}, contact time 0.4 h), 24 mLh^{-1} (WHSV 0.91 h^{-1}, contact time 1.1 h), 12 mLh^{-1} (WHSV 0.48 h^{-1}, contact time 2.1 h), 1.2 mLh^{-1} (WHSV 0.06 h^{-1}, contact time 18 h). 0.6 mLh^{-1} (WHSV 0.02 h^{-1}, contact time 60 h).

Table S1. Performances of noble and non-noble metal heterogeneous catalysts for the hydrogenation of HMF into BHMF.

Catalyst	Solvent	P (bar)	T (°C)	Time (h)	HMF Conv. (%)	BHMF Yield (%)	Ref.
Au/Al_2O_3	Water	65	120	2	100	96	[1]
Pd/C	Tetrahydrofuran/water	100	80	20	97	82	[2]
Pt/C	Ethanol	14	23	18	-	82	[3]
$PtSn/SnO_2/RGO$	Ethanol	20	70	0.5	99	99	[4]
Ru/C	Water	50	60	0.7	100	100	[5]
Ru/ZrO_2	1-butanol	15	120	6	99	99	[6]
Ir/TiO_2	Water	60	50	3	99	95	[7]
Cu/SiO_2	MeOH	25	100	8	100	97	[8]
Cu/PMO	EtOH	50	100	3	100	99	[9]
Cu/ZnO	1,4-dioxane	15	100	2	100	99	[10]
Raney Cu	H_2O	90	90	8	94	86	[11]
CuZn	EtOH	70	120	3	100	95	[12]
Raney Ni	H_2O	90	90	8	100	60	[11]
NiFe/CNT	1-butanol	30	110	18	100	96	[13]
CoAl[a]	MeOH	40	120	4	89	83	[14]
Co/SiO_2	H_2O	34	60	4	100	96	[15]
Raney Co	MeOH	40	120	4	100[b]	0	[14]
Raney Co	MeOH	20	120	1	100	94.5	[16]
Co-400[c]	MeOH	20	90	1	94	93	[16]
Co@C	MeOH	10	110	2	97	96	this work

[a] Co alumina mixed oxide. [b] *The main product was* 2,5-bis(hydroxymethyl)tetrahydrofuran. [c] Co-400 is a commercial Co_3O_4 reduced at 400 °C.

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